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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 401/04, 405/04, 409/04 — A1

(11) International Publication Number: WO 91/07398

(43) International Publication Date: 30 May 1991 (30.05.91)

(21) International Application Number: PCT/DK90/00304

(22) International Filing Date: 22 November 1990 (22.11.90)

(30) Priority data:
5882/89 22 November 1989 (22.11.89) DK

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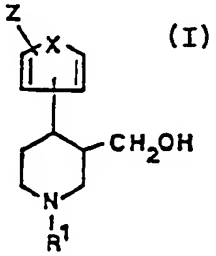
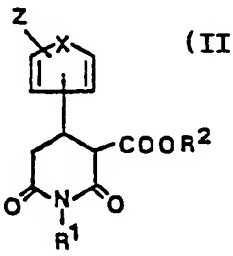
(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent).

Published
With international search report.

(54) Title: 4-HETEROARYL PIPERIDINE INTERMEDIATES AND THEIR PREPARATION



(I)



(II)

(57) Abstract

This invention relates to new compounds of formulae (I, II) in which X is O, S, or NR where R is H or C_{1-4}-alkyl, Z is hydrogen, halogen, trifluoromethyl, C_{1-8}-alkoxy, C_{1-8}-alkyl straight or branched, nitro, C_{2-8}-alkenyl, or a C_{1-4}-alkyl mono- or disubstituted amino group, R^1 is H or straight or branched C_{1-8}-alkyl. The invention also relates to a method of preparing a compound of formulae (I and II).

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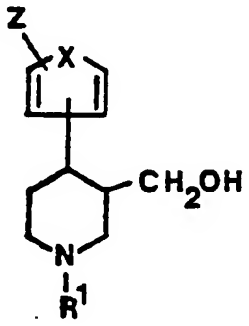
4-HETEROARYL PIPERIDINE INTERMEDIATES AND THEIR PREPARATION

This invention relates to a novel chemical process for preparing new heteroaryl piperidine carbinols and to novel intermediates used in that process.

The novel compounds are useful as intermediates in processes leading to pharmacological active substances.

This invention relates to new compounds of formula I



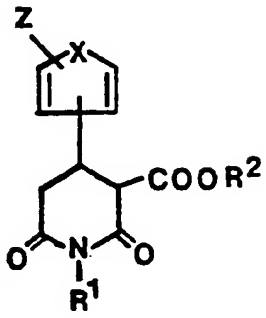
I

in which X is O, S, or NR where R is H or C_{1-4}-alkyl, Z is hydrogen, halogen, trifluoromethyl, C_{1-8}-alkoxy, C_{1-8}- alkyl straight or branched, nitro, C_{2-8}-alkenyl, or a C_{1-4}-alkyl mono- or disubstituted amino group, R^1 is H or straight or branched C_{1-8}-alkyl.

The invention also relates to a method of preparing a compound of formula I.

This method which uses easily accessible commercially available starting materials comprises:

a) preparation of a compound of formula II



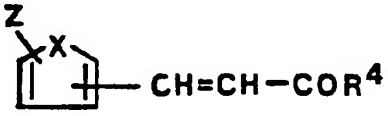
II

wherein X, Z, R and R^1 have the meaning defined above and R^2 is C_{1-2}-alkyl,

by reacting a compound of formula IV

$$R^3OCH_2COOR^2 \qquad \text{IV}$$

with a compound of the formula V

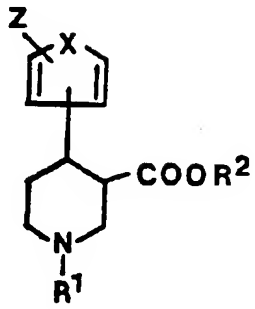


V

under basic conditions eg. using alkoxide in ethanol, wherein X, Z, R, R^1 and R^2 have the meaning defined above and R^3 being C_{1-2}-alkoxy when R^4 is NHR^1 or R^3 being NHR^1 when R^4 is C_{1-2}-alkoxy,

b) reduction of a compound of formula II wherein X, Z, R, R^1 and R^2 have the meaning defined above, with metal hydride eg. $LiAlH_4$ or AlH_3 in ether or THF giving a compound of formula I wherein X, Z, R and R^1 have the meaning defined above,

c) reduction of a compound of formula III



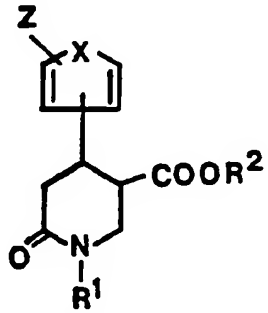
III

wherein X, Z, R, R^1 and R^2 have the meaning defined above with a metal hydride eg. $LiAlH_4$ or AlH_3 giving a compound of formula I wherein X, Z, R and R^1 have the meaning defined above;

compounds of formula III can be prepared conveniently from Arecoline-type derivatives and metal organic derivatives of heteroaromates using well known procedures,

d) compounds of formula I may also be prepared by reacting compounds of formula I wherein Z is H, with reagents causing heteroaromatic substitution using well known procedures,

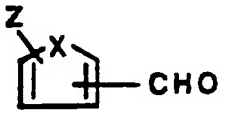
e) compounds of formula I may be prepared by metal hydride reduction of a compound of formula VI



VI

wherein X, Z, R, R^1 and R^2 have the meaning defined above,

f) compounds of formula II may be prepared in a one pot reaction using a compound of formula VII wherein X, Z and R have the meaning defined above



VII

as starting material. The reaction is carried out using ethyl acetate as solvent and methoxide or ethoxide as base. After initial reaction between VII and solvent a compound of formula VIII wherein R^1 and R^2 have the meaning defined above,

$$R^2OOCCH_2CONHR^1 \qquad \text{VIII}$$

is added resulting in the formation of compounds of formula II wherein X, Z, R, R^1 and R^2 have the meaning defined above.

The invention will now be described in further detail with reference to the following examples.

EXAMPLE 1

3-hydroxymethyl-1-methyl-4-(2-thienyl)-piperidine (1)

3-methoxycarbonyl-1-methyl-4-(2-thienyl)-piperidine (2) was prepared from Arecoline, HBr (52 g), 2-bromothiophene (41 ml) and Mg-turnings (9.9 g) as described by Plati et. al. (J. Org. Chem. 22 (1957) 261). The resulting proudct was purified by distillation giving 15 g cis/trans mixture b.p. 50-120°C / 1.1 mm Hg.

30 g of this product was reduced with $LiAlH_4$ (5 g) in dry ether (200 ml) by reflux for 30 min. in N_2-atmosphere. The well known rinse up procedure gave a hard

oil (21 g) identified as 3-hydroxymethyl-1-methyl-4-(2-thienyl)-piperidine(1) by ^{1}H NMR ($CDCl_3$), : 6.7 - 7.3 (3H,m); 3.8- 4.5 (1H,broad) 3.5-3.7 (2H,m); 2.8-3.5 (3H,m); 2.2 (3H,s); 1.8-2.8 (5H,m)

EXAMPLE 2

3-(2-thienyl)-propenoyl chloride (3) was prepared by dropwise addition of thionyl chloride (50 ml) to 3-(2-thienyl)-propenoic acid (25 g) and subsequent heating to 60°C for 2 hours. Excess of $SOCl_2$ was evaporated in vacuo, CH_2Cl_2 was added and the reaction mixture was evaporated to dryness yielding 28 g of (3).

N-pentyl-3-(2-thienyl)-propenoic amide (4) was prepared from (3) (28 g) dissolved in dry toluene (200 ml) pentyl amine (25 ml) and triethyl amine (70 ml) was added under cooling (ice bath). Stirring for 1 hour. The precipitate of triethylammonium chloride was removed by filtration, the filtrate was evaporated to dryness and the resulting mass treated with ether giving (4) as colourless crystals (22.8 g). ^{1}H NMR ($CDCl_3$), : 0.7-1.1 (3H,m); 1.1-1.7(6H,m); 3.0-3.4 (2H, dist.q), 6.2-8.2 (6H,m).

3-ethoxycarbonyl-1-pentyl-4-(2-thienyl)-piperidine 2,6-dione (5)

Sodium (3 g) was dissolved in abs. ethanol (60 ml), diethyl malonate (20 ml) dissolved in abs. ethanol (30 ml) was added followed by a slurry of (4) (22.8 g) in abs. ethanol (50 ml). Reflux for 4 hours, the ethanol was evaporated, toluene added (100 ml), and the reflux continued overnight. After cooling the formed precipitate was isolated, dissolved in 1M HCl and extracted several times with ether. The combined ether phases were evaporated giving an oil which was purified on silica gel using CH_2Cl_2/CH_3OH 9/1 as eluent. Yield

22.6 g of (5) as an oil identified by ^{1}H NMR ($CDCl_3$), : 0.7-0.95 (3H,m); 1.0-1.5 (9H,m); 2.9-3.2 (2H,m) 4.15 (2H,q); 3.6-4.15 (4H,m); 6.8-7.2 (3H,m).

3-hydroxymethyl-1-pentyl-4-(2-thienyl)-piperidine (6) was prepared from (5) (22.6 g) by reduction with $LiAlH_4$ (13 g) in dry THF. Reflux for 3 hours under N_2. Using the well known work up procedure gave a hard oil (4 g) identified by ^{1}H NMR ($CDCl_3$), : 0.7-1.1 (3H,m); 1.1-1.7 (6H,m); 1.7-2.1 (4H,m); 2.1-3.9 (9H,m); 6.8-7.2 (3H,m).

EXAMPLE 3

N-pentyl-3-(3-thienyl)-propenoic amide (7) was prepared as described for (4). ^{1}H NMR ($CDCl_3$), : 0.7-1.1 (3H,m); 1.1-1.7 (6H,m); 3.2-3.6 (2H, dist. q); 6.1-7.8 (6H,m).

3-ethoxycarbonyl-1-pentyl-4-(3-thienyl)-piperidine-2,6-dione (8) was prepared as described for (5). 32 g (7) gave 41 g of crude (8) which was used without further purification. Reduction and work up as described for the preparation of (6) gave 7.7 g of crystalline 3-hydroxymethyl-1-pentyl-4-(3-thienyl)-piperidine (9). M.p. 96.5-97.5°C.

EXAMPLE 4

(±)-1-butyl-3-ethoxycarbonyl-4-(2-thienyl)-2,6-piperidinedione (10)

A solution of 2-thiophenecarbaldehyde (22.4 g) in ethyl acetate (20 ml) was added to a slurry of sodium ethanolate (32.6 g) in ethyl acetate (200 ml). The temperature was kept at 10°C and the mixture stirred for one hour. A solution of ethyl N-butylamidomalonate (41.2 g) in

ethyl acetate (40 ml) was slowly added to the mixture whilst keeping the temperature below 5°C. The mixture was stirred for 18 hours at 20°C and neutralized with 25% acetic acid (130 ml). The water phase was discharged and the organic phase extracted twice with saturated sodium chloride solution (2x50 ml). The organic phase was evaporated, the residue dissolved in toluene (200 ml), dried with potassium carbonate and evaporated to give the crude product. Yield 72 g of an oil identified by ^{1}H NMR ($CDCl_3$), : 0.7-1.4 (10H,m); 2.7-4.2 (8H,m); 6.7-7.3 (3H,m).

(±)-1-butyl-3-hydroxymethyl-4-(2-thienyl)-piperidine (11)

A solution of crude (±)-1-butyl-3-ethoxycarbonyl-4-(2-thienyl)-2,6-piperidindione (72 g) in toluene (100 ml) was added to a slurry of $LiAlH_4$ (15.2 g) in THF (100 ml) and toluene (50 ml). The temperature was kept below 10°C during the addition. The reaction mixture was stirred for 18 hours and decomposed by careful addition of water (75 ml) keeping the temperature below 10°C. The hydrolyzed mixture was stirred for 1 hour before the precipitated salts was filtered off. The filtrate was evaporated to give an oil (33 g) which was recrystallized from ethyl acetate (50 ml), filtered off and dried to give the title compound (17 g), m.p. 89.7-90.1°C.

EXAMPLE 5

(+-)-1-butyl-3-ethoxycarbonyl-4-(5-methyl-2-furanyl)-2,6-piperidinedione (12)

was prepared from 5-methyl- 2-furancarbaldehyde (22 g) as described for compound (10). Yield 59.5 g of an oil (80% pure by HPLC). Identified by ^{1}H NMR ($CDCl_3$) : 0.7-1.6 (10H, m), 2.2 - 2.4 (3H, d); 2.8 - 4.5 (8H, m);

5.8-7.5 (2H, m).

(+-)-1-butyl-3-hydroxymethyl-4-(5-methyl-2-furanyl)-piperidine (13) was prepared from crude (12) (59 g) by reduction with $LiAlH_4$, as described for (11). Yield 22 g of (13). M.p. 83.5°C.

EXAMPLE 6

(+-)-1-butyl-3-ethoxycarbonyl-4-(1-methyl-2-pyrrolyl)-2,6-piperidinedione (14)

was prepared from 1-methyl-2-pyrrolecarbaldehyde (10.2 g) and ethyl N-butylamidomalonate (15.4 g) in ethyl acetate as described for compound (10). The crude product (27 g) was subsequently reduced without further purification as described for compound (11). Yield 14 g of

(+-)-1-butyl-3-hydroxymethyl-4-(1-methyl-2-pyrrolyl)-piperidine (15) precipitated as the oxalate. ^1H NMR ($CDCl_3$) : 0.7-1.1 (3H, m); 1.1 - 2.2 (6H, m); 2.5 - 3.8 (10H, m), 3.5 (3H, s), 5.7 - 6.0 (2 H, m); 6.1 - 6.7 (1H, m).

EXAMPLE 7

3-Ethoxycarbonyl-1-(2-methylbutyl)-4-(3-thienyl)-2,6-piperidinedione (16)

was prepared from 3-thiophenecarbaldehyde (20 g) and ethyl N-(2-methylbutylamidomalonate) (35 g) in ethyl acetate as described for compound (10). The crude product (60 g oil) was reduced in THF by means of $LiAlH_4$ as described for compound (11) giving

3-hydroxymethyl-1-(2-methylbutyl)-4-(3-thienyl)-

piperidine (17)

The crude product (23 g) was purified on silica gel using ethyl acetate as eluent.

Mass spectrum (M^+: 267) degradation in accordance with proposed structure. m.p. 88.8-90.2°C.

EXAMPLE 8

The following compounds were prepared exactly as described for (17) using the appropriate substituted thiophenecarbaldehyde and ethyl amidomalonate. The dione intermediate was used without purification.

3-hydroxymethyl-1-pentyl-4-(2-thienyl)piperidine (18)

Yield 17.6%; m.p. 107.6°C.

1-butyl-3-hydroxymethyl-4-(2-thienyl)piperidine (19)

Yield 27.2%; m.p. 90.9°C.

1-butyl-3-hydroxymethyl-4-(3-thienyl)piperidine (20)

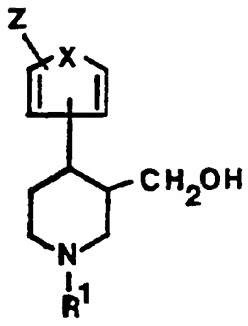
Yield 27.9%; m.p. 81.7°C.

3-hydroxymethyl-1-pentyl-4-(3-thienyl)piperidine (21)

Yield 27.5%; m.p. 93.9°C.

CLAIMS

1) A process for the preparation of a compound of formula I

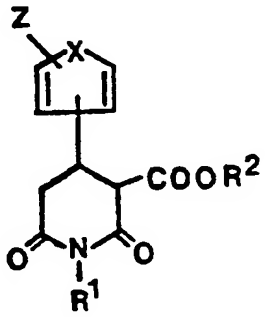


I

wherein X is O, S or NR, R is H or C_{1-4}-alkyl, Z is hydrogen, halogen, trifluoromethyl, C_{1-8}-alkoxy, straight or branched C_{1-8}-alkyl, nitro, C_{2-8}-alkenyl, or a C_{1-4}-alkyl mono- or disubstituted amino group,

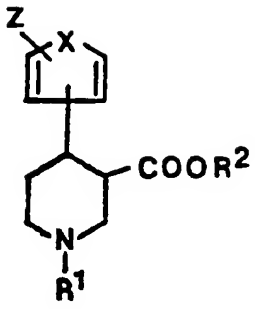
R^1 is H, straight or branched C_{1-8}-alkyl;

the process comprises a preparation and reduction of a compound of formula II with a metal hydride eg. $LiAlH_4$



II

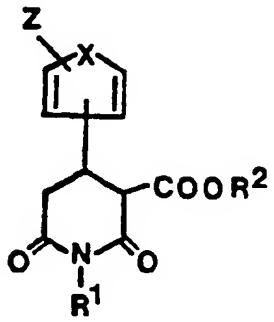
wherein X, Z, R and R^1 is defined above and R^2 is C_{1-2}-alkyl and the preparation and reduction of a compound of formula III by means of metal hydride eg. $LiAlH_4$



III

wherein X, Z, R, R^1 and R^2 have the meaning defined above

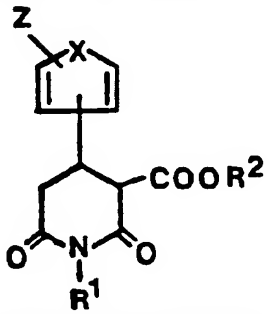
2) a compound of formula II



II

wherein X, Z, R, R^1, and R^2 have the meaning defined above

3) a process for the preparation of a compound of formula II

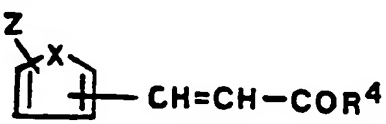


II

wherein X, Z, R, R^1 and R^2 have the meaning defined above, which comprises reacting a compound of formula IV

$$R^3OCCH_2COOR^2 \qquad \text{IV}$$

with a compound of formula V

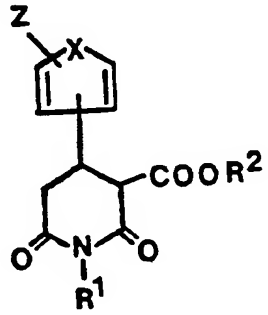


V

under basic conditions, wherein

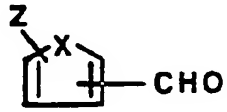
X, Z, R, R^1 and R^2 have the meaning defined above, R^3 being C_{1-2}-alkoxy when R^4 is NHR^1 or R^3 being NHR^1 when R^4 is C_{1-2}-alkoxy.

4) a process for the preparation of a compound of formula II



II

wherein X, Z, R, R^1 and R^2 have the meaning defined above, which comprises reacting of a compound of formula VII



VII

wherein X, Z and R have the meaning defined above, with a compound of formula VIII

$$R^2OOCCH_2CONHR^1 \qquad \text{VIII}$$

wherein R^1 and R^2 have the meaning defined above, in ethyl acetate using ethoxide or methoxide as base.

5) a compound which is 3-ethoxycarbonyl-1-pentyl-4-(2-thienyl)-piperidine-2,6-dione.

6) a compound which is 3-hydroxymethyl-1-methyl-4-(2-thienyl)-piperidine.

7) a compound which is 3-hydroxymethyl-1-pentyl-4-(3-thienyl)-piperidine.

8) a compound which is 3-ethoxycarbonyl-1-pentyl-4-(3-thienyl)-piperidine-2,6-dione.

9) a compound which is 3-methoxycarbonyl-1-methyl-4-(2-thienyl)-piperidine.

10) a compound which is 3-hydroxymethyl-1-pentyl-4-(2-thienyl)piperidine

11) a compound which is 1-butyl-3-hydroxymethyl-4-(2-thienyl)piperidine

12) a compound which is 1-butyl-3-hydroxymethyl-4-(5-methyl-2-furanyl)piperidine

13) a compound which is 1-butyl-3-hydroxymethyl-4-(3-thienyl)piperidine

14) a compound which is 3-hydroxymethyl-1-(2-methyl-butyl)-4-(3-thienyl)piperidine

15) a compound which is 1-butyl-3-hydroxymethyl-4-(1-methyl-2-pyrrolyl)piperidine.

INTERNATIONAL SEARCH REPORT

International Application No PCT/DK 90/00304

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 D 401/04, 405/04, 409/04

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

SE,DK;FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP, A1, 0223334 (BEECHAM GROUP PLC) 27 May 1987, see the whole document --	1-15
X	EP, A2, 0190496 (BEECHAM GROUP PLC) 13 August 1986, see pages 1-19	1,3
A	--	2,5-15
A	US, A, 4007196 (JORGEN ANDERS CHRISTENSEN ET AL.) 8 February 1977, see the whole document --	6-7,9-15
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* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
27th February 1991	1991 -03- 0 6
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	Göran Karlsson

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers ...2 and 5-15..... because they relate to subject matter not required to be searched by this Authority, namely:

See annexed sheet !

2. [ ] Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED [illegible]

Claims 2 and 5-15 can not be fully searched and categorized because the structure and the use of the pharmacological active substances are not specified in the description. According to Article 5, the description shall disclose the invention in a manner sufficiently clear and complete for the invention to be carried out by a person skilled in the art.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.PCT/DK 90/00304

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the Swedish Patent Office EDP file on 91-01-31
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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